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The Status of Corticosteroid Therapy In Dermatology

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• Therapy with systemic corticosteroids, despite attendant serious risks, is mandatory in diseases such as pemphigus, acute disseminated lupus erythematosus and some cases of exfoliative dermatitis that are ordinarily fatal, for in such cases life may be prolonged and the patients made comfortable. If no contraindications exist, therapy with corticosteroids is desirable, for diseases of short duration—contact dermatitis, serum sickness reactions and drug eruptions of all kinds—provided the causative factors have been removed and the reactions are causing severe distress.

On the basis of encouraging reports in the literature corticosteroid therapy may be instituted with justification for a group of unrelated, intractable and discomforting diseases such as maddening pruritus ani, sclerema neonatorum, dermatomyositis, certain cases of sarcoidosis, berylliosis, Behcet's syndrome, universal calcinosis, Reiter's disease and ulcers of sickle-cell anemia.

One must always bear in mind the well-defined contraindications to corticosteroid therapy and the hazards of its use, particularly if therapy is to be prolonged.

Results from topical hydrocortisone therapy are particularly pleasing in chronic eczematous otitis externa and especially when it is combined with an antibiotic drug. Results are excellent also in nuchal eczema, dermatitis of the eyelids and in pruritus ani.

More often than not, hydrocortisone ointment and lotions benefit more than do other standard remedies such diseases as atopic eczema, contact dermatitis, lichen simplex-chronicus and eczematized phases of conditions such as psoriasis and superficial mycotic infections. Preparations containing a combination of hydrocortisone and an antibiotic are more useful than hydrocortisone alone.

When used with discrimination, with full attention to the selection of cases and proper concentration in the correct vehicle, hydrocortisone preparations in combination with antibiotics are excellent antieczematous agents.

IT IS NOW approximately five years since the corticosteroids were first made available for general use and specifically recommended for the treatment of rheumatoid arthritis. Very soon, and understandably, steroid therapy was extended to the so-called relatives of arthritis—the collagen group of diseases and diseases of hypersensitivity. And so it was that dermatology in particular felt the impact of this new wonder therapy. As steroid therapy was rapidly extended to more and more diseases, it soon became evident that the therapy had not only assets but limitations and liabilities. Because the drugs are capable of producing profound systemic reactions—some tragic in their consequences—there is still considerable disagreement as to the justification for

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their use for certain conditions. Yet in general they are being employed with ever increasing frequency and for more and more diseases, so that, as some one waggishly remarked recently, "Physicians may be divided into three classes: Those who use ACTH or cortisone for everything, those who never use them for anything, and those who use them only when they are needed."

It would seem that sufficient time has passed to permit the formulation of definitive indications. However, this has proved difficult because of the fact that, although remarkable progress has been made in the fundamental knowledge of the steroids, so much still remains unknown of their actual mode of action. There is still no full explanation as to why one drug is sometimes more effective than the other; still no way of formulating precise dosage; and still insufficient knowledge of the full effects or hazards from prolonged therapy. It would seem that a workable plan could be formulated, for in general the corticosteroids have proved a boon for skin diseases of three general groups: Diseases such as pemphigus or acute disseminated lupus erythematosus that are usually fatal; diseases such as crippling eczema that are not fatal but which may ruin life; and diseases such as discomforting drug eruptions or widespread acute poison ivy dermatitis which are of short duration provided the causative factors have been removed.

There is general agreement that corticosteroid therapy, when combined with both supportive measures and with antibiotic agents to control infection, constitutes the best therapy yet devised for the treatment of pemphigus. Patients with pemphigus are alive today who undoubtedly would not be had corticosteroids not been available. Large dosages are often necessary for patients with pemphigus—as large as 1,000 mg. or more a day of cortisone for a while—and, of course, therapy has to be maintained for long periods despite the risks of Cushing's syndrome, diabetes, psychosis and fractures. These constitute calculated risks which seem important when life itself is at stake, and beneficial effects from the drugs in such cases have thus far greatly outnumbered the incidence of distressing effects. Usually patients with pemphigus respond alike to corticotropin, cortisone or hydrocortisone; but in some instances, and for some unexplained reason, one drug proves effective where the others fail.

Perhaps the most dramatic results from this therapy occur in patients with acute systemic lupus erythematosus, but not in the chronic or subacute forms of the disease. There have been innumerable reports of moribund patients coming to life after a day or two of therapy. The author's first experience with such a case left an indelible impression. The patient was a youngster in her teens who was sadly close to death. The hospital had just received a new drug called ACTH—one of the first supplies of the drug to be released five years ago for experimental purposes only. It was administered to the girl, who was hopelessly moribund, and within 48 hours she was sitting up in bed, talking and alert. At last report, not long ago, she was still in fairly good health. After an experience like that it would be difficult to withhold such treatment from patients with acute systemic lupus erythematosus even though the drugs effect no cure but merely suppress symptoms—and, as with pemphigus, patients eventually die of the disease.

The use of corticosteroid therapy, it would seem, is not only justifiable but often desirable in diseases with reactions of hypersensitivity that are usually self-limited, such as severe drug eruptions, acute angioneurotic edema, erythema multiforme or dermatitis venenata. If the causative factor has been removed (drug discontinued, irritating plant or chemical discarded), quick relief from discomfort can usually be attained by corticosteroid therapy in sufficient dosages. If the eruption is severe, cortisone (or comparable amounts of corticotropin or hydrocortisone) given on a schedule of 300 mg. in divided dosages for 24 hours followed by 200 mg. for a day or two, and then decreasing by 25 or 50 mg. each day, usually effects gratifying relief to the patient. And the entire treatment is complete within a week or two so that risks from it are lessened considerably.

It is with the third group of diseases that a good deal of soul-searching is required before instituting corticosteroid therapy—that group of chronic, nonfatal diseases such as atopic eczema or eczematized psoriasis that become so acute or widespread as to constitute a life-ruining or crippling disease. Long-term therapy is usually necessary for such diseases and the hazards of prolonged therapy may be such as to raise a question as to whether the treatment is justified. Certainly it would seem justified if in the physician's opinion the patient is actually incapacitated, for in such cases therapy for a short period would effect relief enough to restore the patient's usefulness, albeit for a relatively short time. But what of the patient who, because of the comfort obtained, understandably pleads for continued treatment although he can scarcely be classified as being incapacitated? Even the more intelligent patients in those circumstances tend to throw caution to the winds and it is then that the physician's position becomes difficult. But no matter how difficult, it is essential that he assume control of the situation just as he does in prescribing narcotic drugs for alleviating pain. Fortunately, investigators have studied the problem and have supplied a workable slide-

rule. In the field of dermatology, Sulzberger and co-workers[4] recently reported their observations on a group of 35 patients with chronic and recurrent skin diseases in which they attempted to ascertain whether or not prolonged therapy affected three things: either increased tolerance or diminished therapeutic effectiveness; addiction; or ill effects higher in incidence or different in kind from short term medication. It would seem from their experience that long-term therapy for chronic recurrent eczematous eruptions may be instituted justifiably as a calculated risk provided certain precautions are observed—of which more later. Their procedure was to institute dosages large enough—cortisone up to 300 mg. a day in divided doses—to allay symptoms quickly. If necessary the dosage was increased unhesitatingly but then, in order to avoid a rebound-reaction, they reduced it by "feeling" their way, for there is not yet a mathematical guide to dosage. If possible the dosage should be brought below 100 mg. daily relatively soon, for the incidence of reactions tends to increase when doses are higher than 100 or 125 mg. daily. As was to be expected, frequently it was found necessary to increase the dosages for a while in order to care for flareups, but it was found, too, that many of the patients were kept comfortable by dosages as low as 5 mg. of cortisone every second day.

Should the experience of additional observers parallel those of Sulzberger and co-workers—and it appears that they will—it is quite likely that long-term therapy for discomforting diseases may become more widely used despite the misgivings of some experienced investigators. Such misgivings are well founded, for corticosteroid therapy is capable of masking hidden active infections and it may reduce fever and maintain a feeling of well-being in the face of serious infections and destruction of tissue. Some of these unfortunate complications may not manifest themselves until some time after the steroid therapy is begun. It may render perforation of a viscus painless. Such therapy may also produce convulsions and psychotic reactions, severe headache, edema, glycosuria and the oft-mentioned Cushing's changes of moon facies, hirsutism, adiposity, striae, acne and buffalo neck. Fortunately these changes are usually reversible but not the disastrous fractures from the relatively rare osteoporosis.

For such reasons it is essential never to institute corticosteroid therapy unless first ascertaining whether or not the patient has or has had diseases such as diabetes, hypertension, peptic ulcer, pulmonary tuberculosis or personality disorders. If the therapy is to be used for long, it is well to determine the blood cell count, the serum sodium, potassium and calcium levels and the fasting blood sugar level, and to have roentgenograms of the long bones for evidence of decalcification. The patient should have a low salt diet (potassium chloride 4 gm. daily) and weekly blood pressure determinations, weight measurements and urinalysis.

It was inevitable, of course, that a therapy capable of producing dramatic results would be used for many and varied diseases, particularly the hitherto intractable diseases. Corticoids have been tried and found useful for the treatment of herpes gestationes but not for herpes simplex or herpes zoster. In fact, herpes zoster occasionally occurs in patients undergoing treatment with steroids for other conditions. Acute lichen planus, but not the chronic form, is helped by corticosteroids, as is alopecia totalis, but this only for as long as the therapy is being used. For the latter condition one must weigh carefully the possible benefits from therapy against the risks, for therapy might conceivably be a life-long matter. Recalcitrant eruptions of the palms and soles is helped sometimes but not always; and other conditions said to be helped on occasion—but not in all cases—are scleroderma, dermatomyositis, dermatitis herpetiformis, sarcoidosis, intractable pruritus ani, sclerema neonatorum, keratosis blenorrhagicum, berylliosis, Behcet's syndrome, universal calcinosis, incontinentia pigmenti, Reiter's disease and ulcers of sickle cell anemia. Corticosteroid therapy has been highly recommended for the control of generalized pruritus of Hodgkin's disease and it is used also as adjunctive treatment to other therapies for lymphoblastomatous disease. Undoubtedly if all reports were in, the list of diseases treated by corticosteroids would be much longer.

TOPICAL THERAPY

When used topically for the treatment of skin diseases, cortisone was found to be ineffective, but hydrocortisone, which was introduced in 1952, has definite value in the treatment of certain of them. At first the short supply and high cost of the drug limited study to relatively few centers, but the first reports were so encouraging that there are now, according to Witten,[5] more than 35 different preparations available, composed of six chemical forms of hydrocortisone. They are incorporated in some 14 different bases, put up in various concentrations from 0.1 per cent to 5 per cent including six preparations in combination form with antibiotics. Available on the market are preparations of hydrocortisone acetate, free alcohol hydrocortisone and fluorhydrocortisone acetate. Other preparations such as chlorhydrocortisone acetate and hydrocortisone cyclopentyl propionate and fluorhydrocortisone free alcohol are being investigated.

The results from treatment with topical hydrocortisone acetate parallel closely those obtained from

systemic treatment with corticosteroids. They act to block tissue reactions to disease-producing factors. Hence their greatest value is to reduce inflammatory eczematous reactions of various kinds, such as atopic eczema, eczema ani, contact dermatitis—particularly on the eyelids—lichen simplex chronicus and sometimes seborrheic eczema. As occurs with systemic therapy, chronic diseases in general soon relapse when the ointment is discontinued and on occasion rebound so actively as to leave the patient in a condition worse than before therapy. On occasion, too, a most satisfactory result from its use is observed, particularly in atopic eczema where the symptoms are suppressed as long as the ointment is used. Then there are instances in which beneficial results would be expected from the therapy but the results are disappointing.

It was feared at first that the topical application of hydrocortisone, like systemically used corticosteroids, would be dangerous in the presence of secondary bacterial or mycotic infections. This has not been borne out. In fact, ointments combining hydrocortisone and antibiotics have given superior results in superficial infections with the possible exception of herpes simplex. Primary irritation or sensitization-reactions from hydrocortisone ointment appear to pose no problem. In the few cases in which irritation has occurred it apparently was due to the base, but of most importance there has been to date no evidence of undesired systemic complications from relatively prolonged use of hydrocortisone acetate or free alcohol-type ointment in the dosages employed. As Lorincz[2] pointed out, however, because of its convenience and rapid symptomatic effects, many patients may be committed to hydrocortisone ointment who will become dependent on it for relief and who may continue to use it for long periods. The ointment has had extensive use for only a little more than a year so that the hazards to the skin from long-term use, if any, have not yet been determined in a sufficient number of cases. "As sign-posts of caution we should keep in mind the well known degenerative effects produced in connective tissue by intradermal hydrocortisone injections,[1] and the observations of Piccagli et al.[3] on the synergistic effect of systemic cortisone administration in mice on epidermal carcinogenesis induced with methylcholanthrene. Thus we might ask—what, if any, is the risk of inducing connective tissue degeneration and consequent premature aging of the skin by prolonged topical hydrocortisone therapy—and what, if any, is the risk of enhancing the development of malignant changes in the skin by such long-term use of topical hydrocortisone."

These risks, even if they are more theoretic than real, should have the attention of investigators, for the employment of hydrocortisone preparations for topical therapy is increasing constantly. Indeed, we are in a period of too-reckless use that may well result in disappointment with a drug that does have undoubted value if used with discrimination. To use it indiscriminately in place of other well established modalities must lead to disappointment. Such factors as the use of an ointment when a wet dressing is indicated, the failure to remove causative irritants when possible, neglect in employing a proper vehicle, failure to adjust to a proper dosage, all contribute to disappointing results. The use of hydrocortisone ointment on noneczematous lesions also constitutes indiscriminate use, for hydrocortisone ointment has no value when applied to common conditions such as psoriasis, discoid lupus erythematosus, lichen planus, alopecia areata, keratoses or warts.

We at Northwestern University recently completed a study of some 1,200 patients treated topically with hydrocortisone acetate in different concentrations and in various vehicles.* Whenever possible, simultaneously paired comparisons were made, using hydrocortisone preparation on one side of the body and the base—or sometimes an old standard-type ointment—on a similar lesion on the opposite side. The results were rather similar to those already noted in other reports. A good response from the ointment was obtained in approximately two-thirds of the cases of atopic and infantile eczema, in contact dermatitis and in localized neurodermatitis—a ratio just a little better than that obtained by older effective therapy. The effects were superior to older methods in dermatitis involving the eyelids, in nuchal eczema and especially in chronic eczematous otitis externa. In acute poison ivy dermatitis, hydrocortisone-antibiotic suspension effected excellent results, but not the ointment. And the suspension was effective also in eczematous eruptions involving the axillae and crural areas. The response to hydrocortisone ointment was highly satisfactory in anogenital pruritus, but more so in pruritus ani than pruritus vulvae. Hydrocortisone was less effective in nummular eczema, seborrheic dermatitis and infectious eczematoid dermatitis, although on occasions dramatic results were observed in all three of these conditions. It should be mentioned that favorable results were not invariably obtained in any disease, not even in contact dermatitis of the eyelids.

It was noted that a concentration of 1 per cent hydrocortisone acetate ointment in a base of liquid paraffin, petrolatum, cholesterol and multiwax was adequate for routine use. It was superior to 0.5 per cent ointment but occasionally was inferior to 2.5 per cent concentration. Sometimes a cream-type

*The materials for this study were supplied by the Upjohn Co., Kalamazoo, Mich.

base was more desirable than the ointment and the suspension was better for use on widespread areas, in hairy areas and in folds such as the axillae and groins. Preparations containing hydrocortisone and neomycin appeared to be a little more effective than hydrocortisone alone. No difference in the results as between the acetate and the free alcohol preparations was observed. Neither proved irritating. Both had only a localized action. The fluorohydrocortisone ointment about which there is at present some uncertainty as to whether it is free of systemic effect, was not used.

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